mary lymphedema (clinical classification).

Diagnosis	Frequency[22,31,32,39] (% of all primary forms)
Congenital (onset <2 years after birth)	6–12
Familial, autosomal dominant (Nonne–Milroy disease)	
Familial, non-dominant inheritance	
Sporadic (most common congenital form)	
Lymphedema precox (onset between 2–35 years)	77–94
Familial, autosomal recessive (Meige disease)	
Sporadic (83–94% of all lymphedema precox)	
Lymphedema tarda (onset after 35 years of age)	11

Figure 1A

. Functional Classification of Primary Lymphedema

	Distal Obliteration (80%)	Proximal Obliteration (10%)	Hyperplasia* (10%)
Gender	Female	Male or female	Male or female
Onset			
Time	Puberty	Any age	Congenital
Location	Ankle; bilateral	Whole leg, thigh; unilateral	Whole leg; unilateral or bilateral
Progression	Slow	Rapid	Progressive
Family history	Frequently positive	None	Frequently positive

Adapted from Browse NL: The diagnosis and management of primary lymphedema. J Vasc Surg 3:181, 1986.
**With or without reflux of chyle.*

Figure 1B

. Secondary lymphedema.

Blockade at the level of the lymph node
- Regional lymph node dissection
  - Axillary (post-mastectomy lymphedema)
  - Pelvic and para-aortic (leg and groin lymphedema)
  - Neck (head and neck lymphedema)
- Neoplastic disease
  - Hodgkin lymphoma
  - Metastatic cancer
  - Prostate cancer
  - Cervical cancer
  - Breast cancer
  - Melanoma

Disruption or obliteration of lymphatic channels
- Surgery, e.g. ilio-femoral bypass
- Direct injury, e.g trauma of the medial aspect of the thigh
- Radiation-induced fibrosis
- Neoplastic infiltration of lymphatic channels
- Rheumatoid arthritis
- Filariasis
- Recurrent infection, e.g. erysipelas

Figure 1C

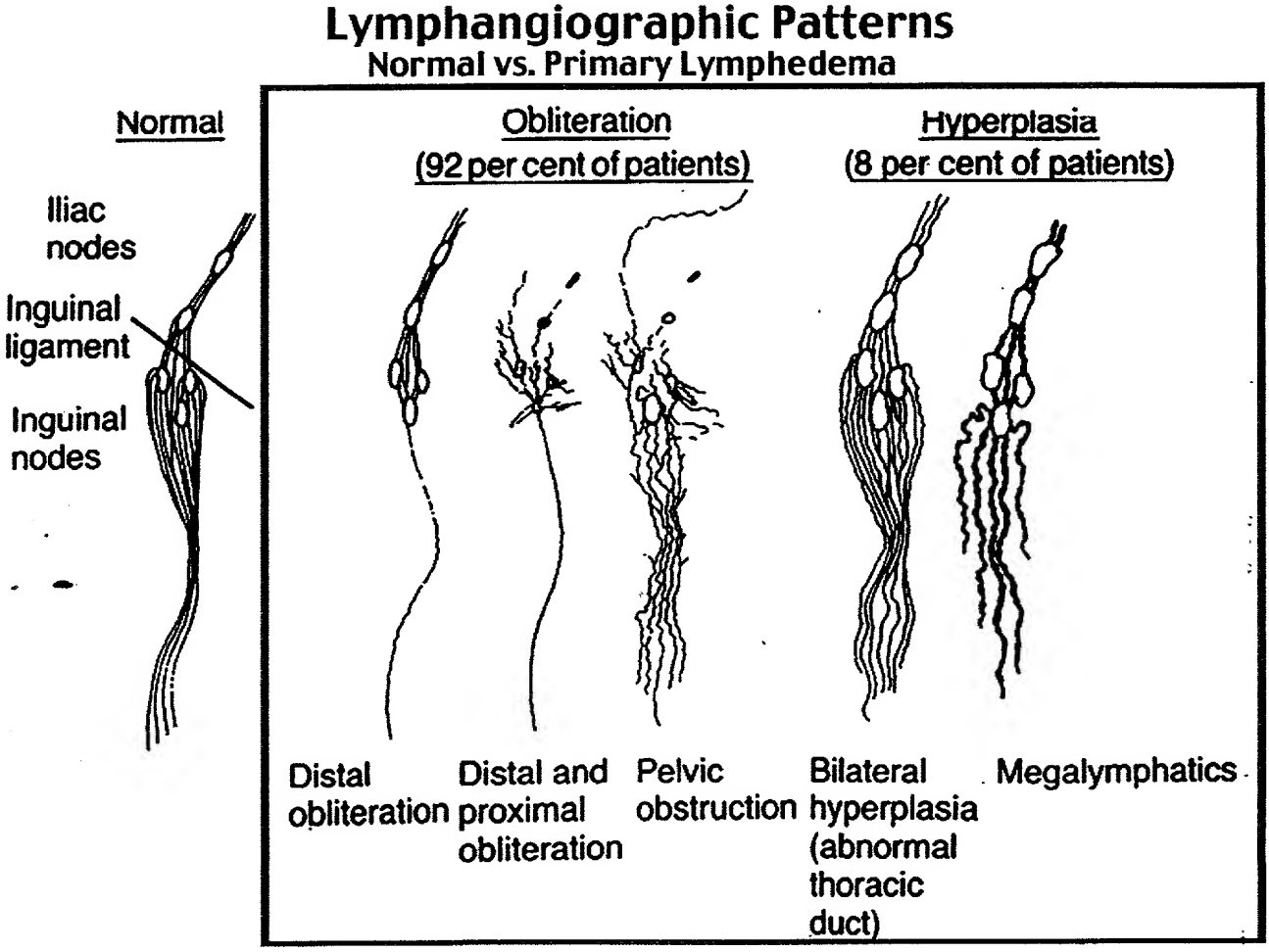


Figure 2

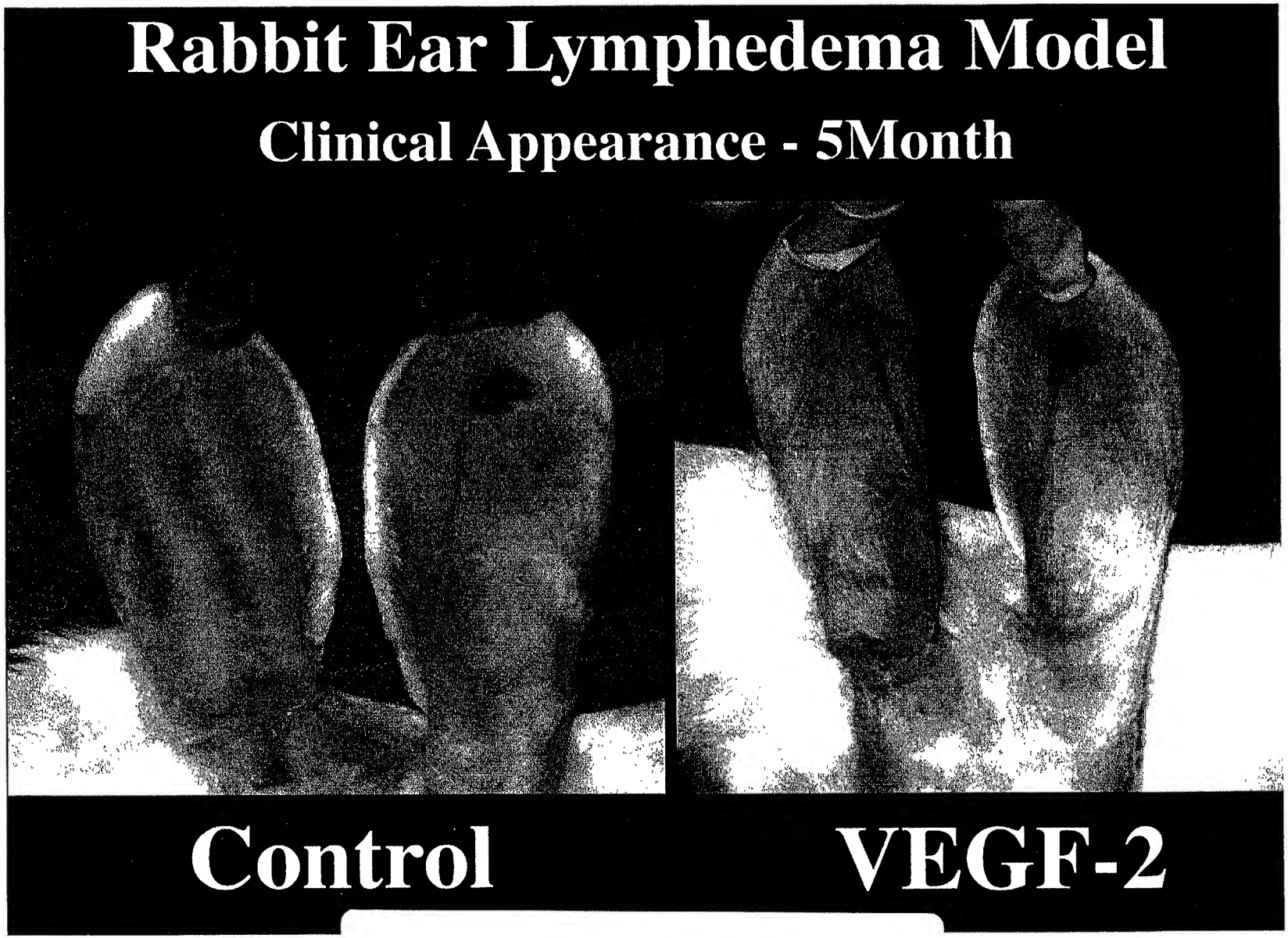

Rabbit Ear Lymphedema Model
Clinical Appearance - 5Month
Control
VEGF-2

Figure 3

Rabbit Ear Lymphedema Model
Lymphoscintigraphy - 5 Month Post-Op

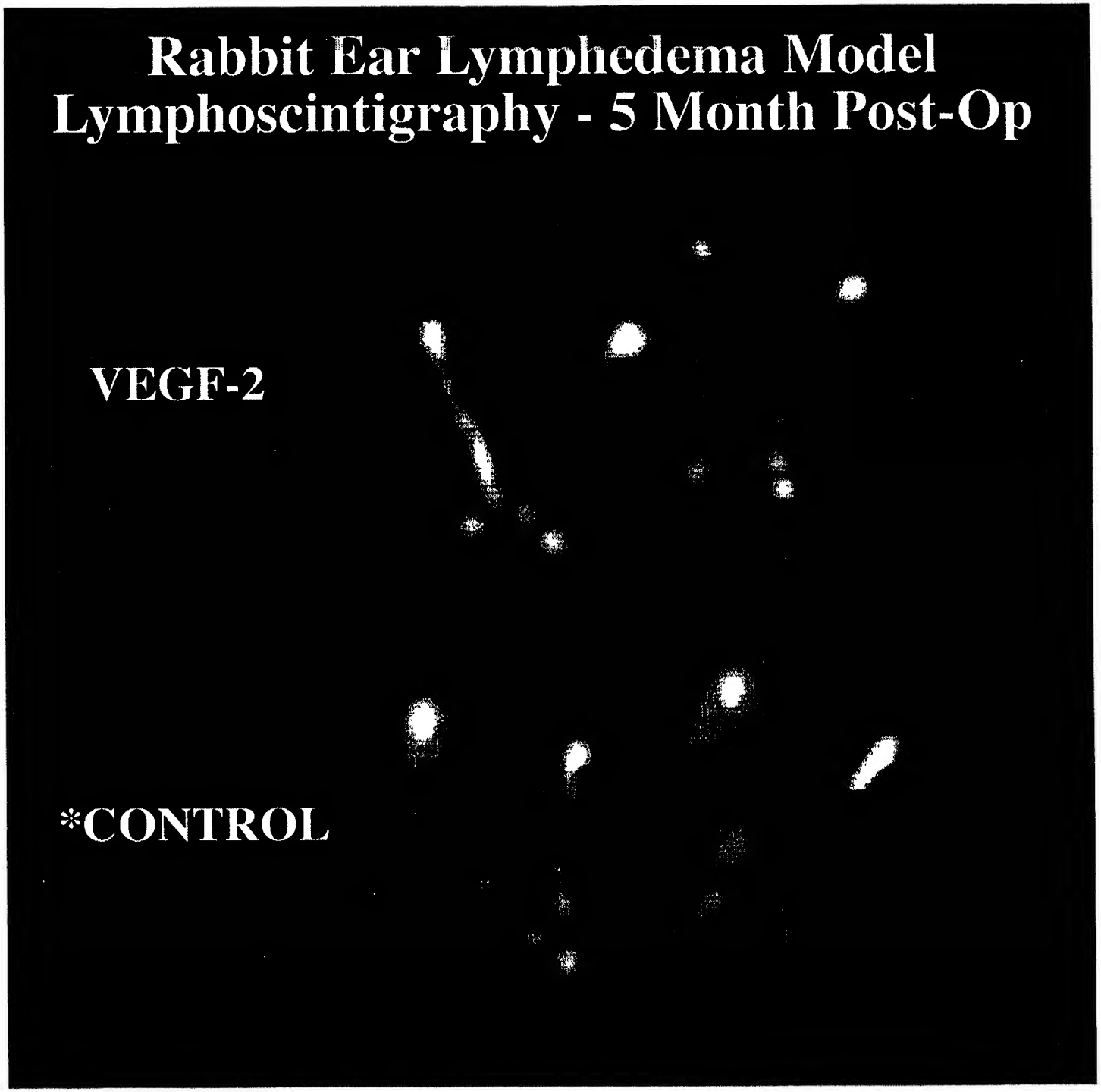


Figure 4

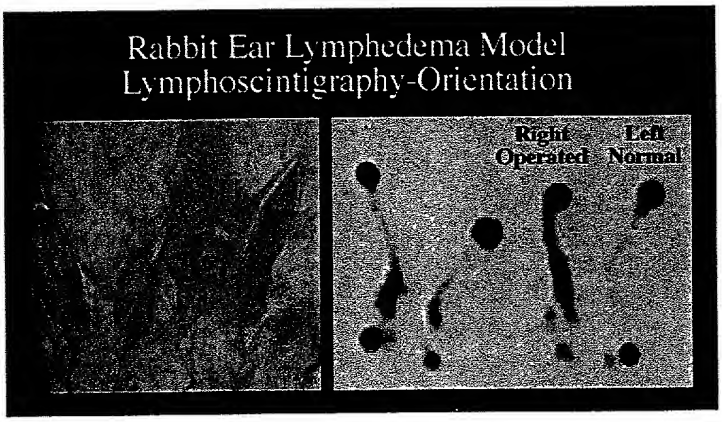

Rabbit Ear Lymphedema Model
Lymphoscintigraphy-Orientation
Right
Operated
Left
Normal

Figure 5

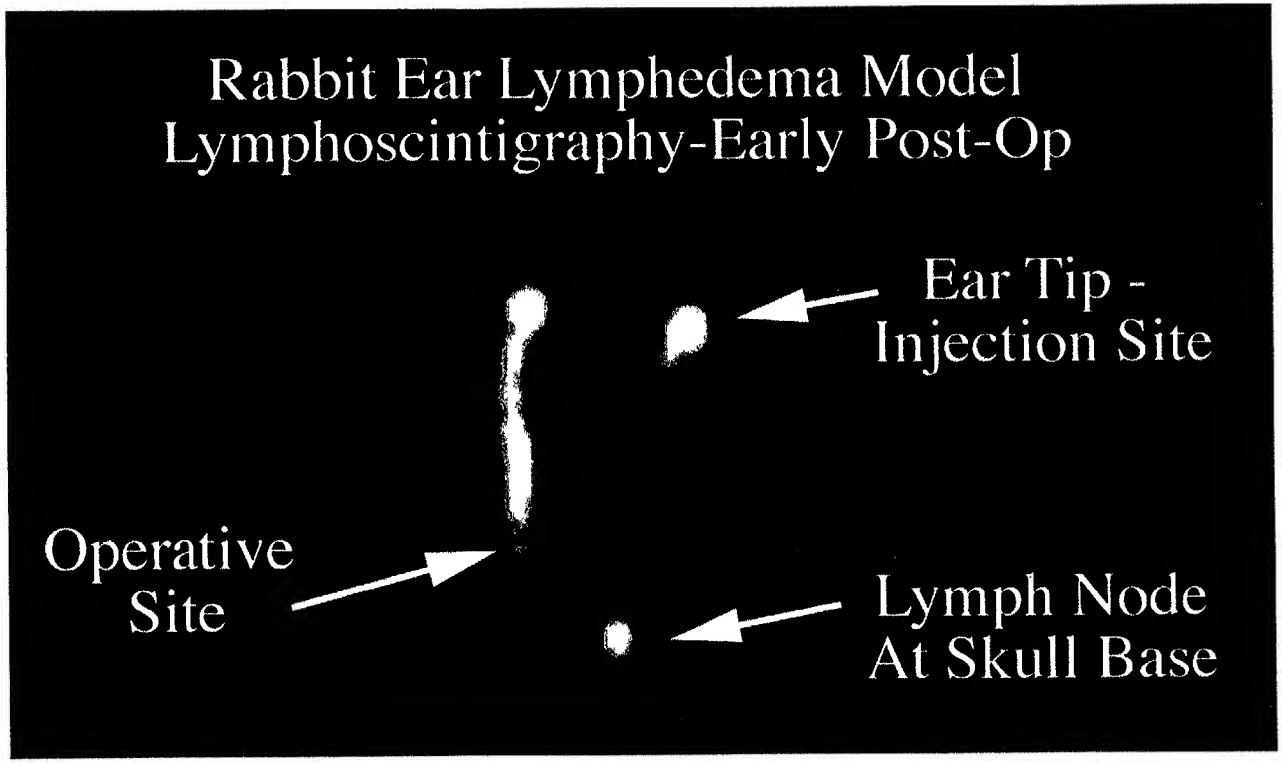


Figure 6

EAR VOLUME

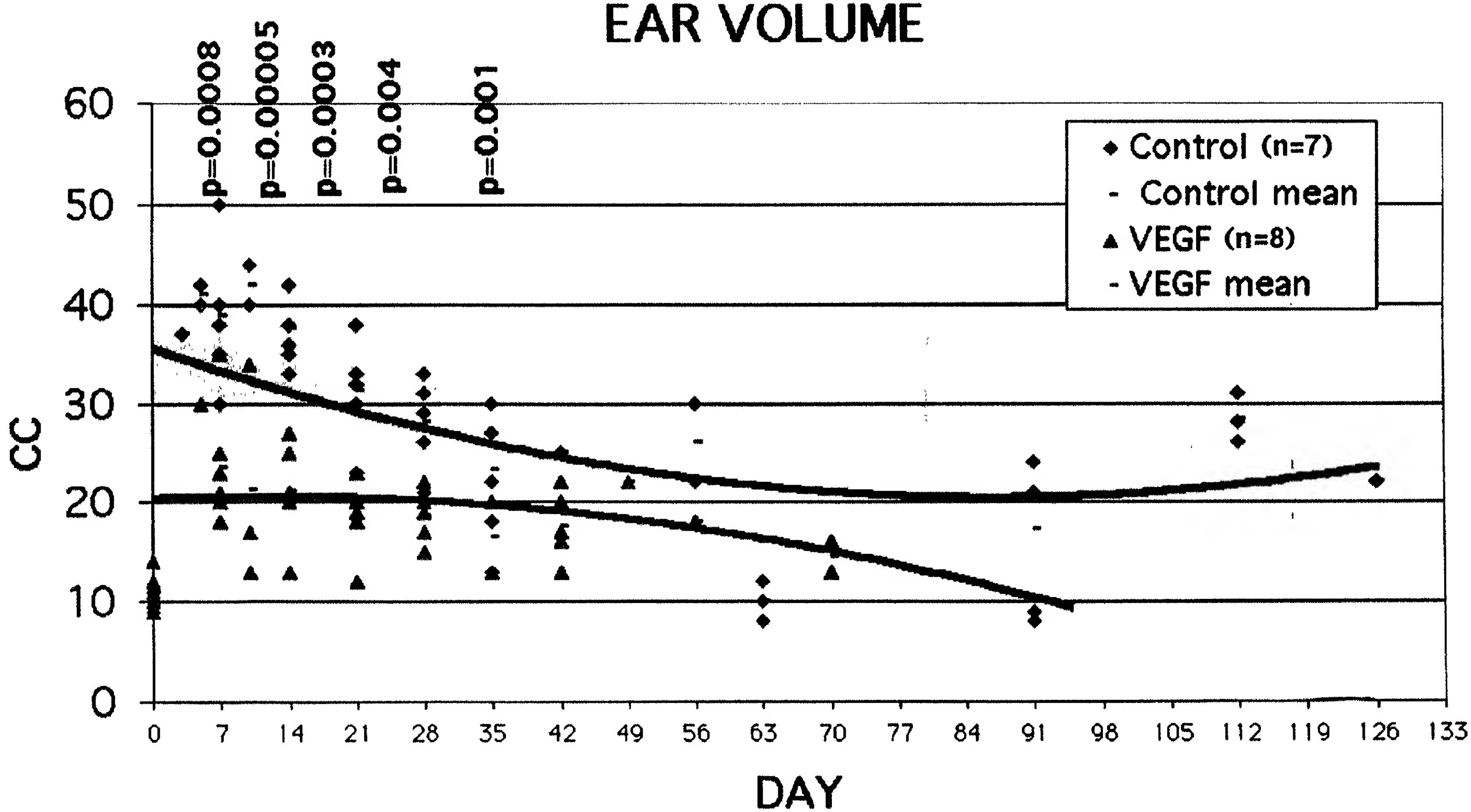


Figure 7

Rabbit Ear Lymphedema Model
3 Days Post-Op

Figure 8

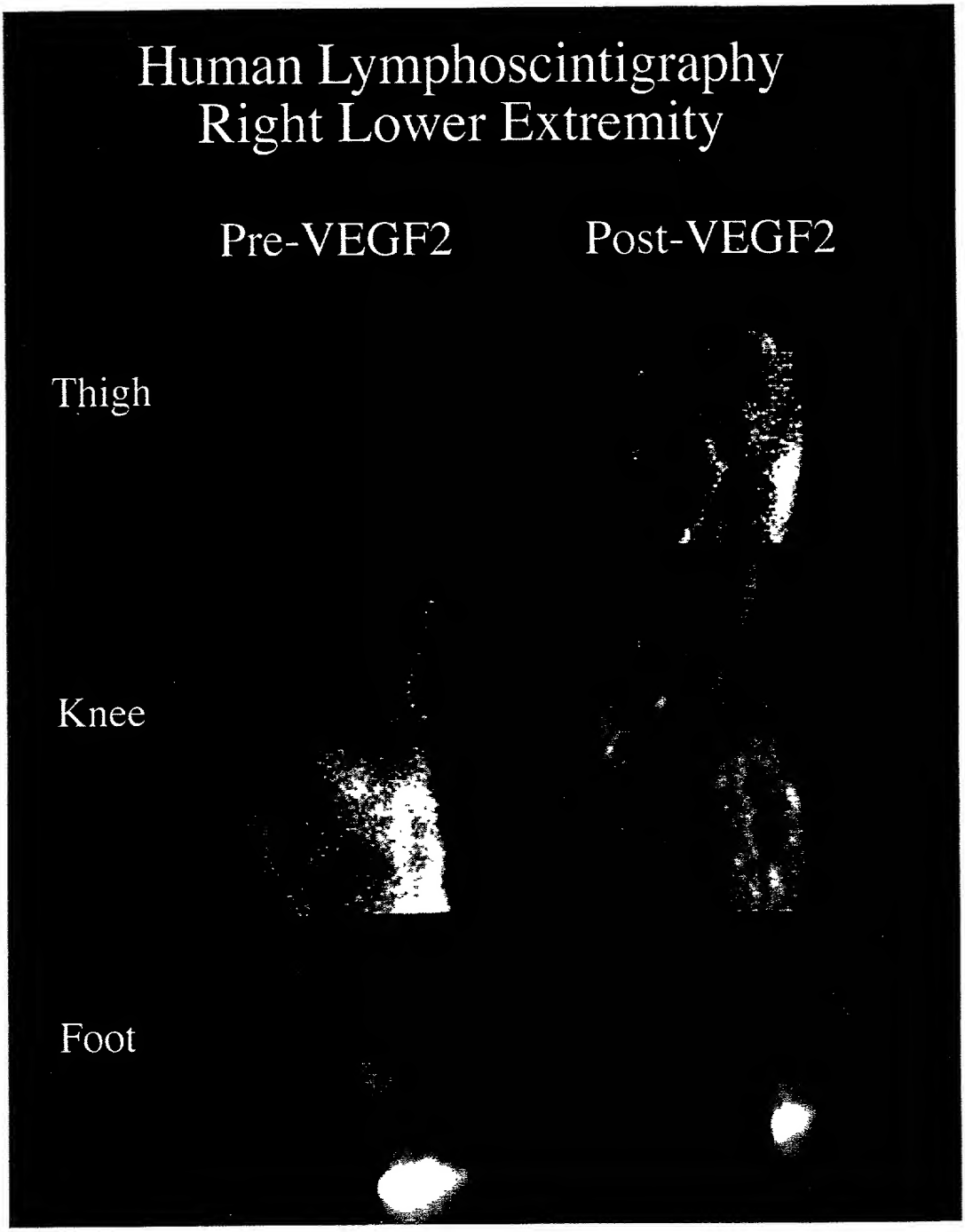

Human Lymphoscintigraphy
Right Lower Extremity
Pre-VEGF2
Post-VEGF2
Thigh
Knee
Foot

Figure 9

Ultrasound Imaging of Intra-Muscular VEGF-2 Gene Transfer: Lymphedema

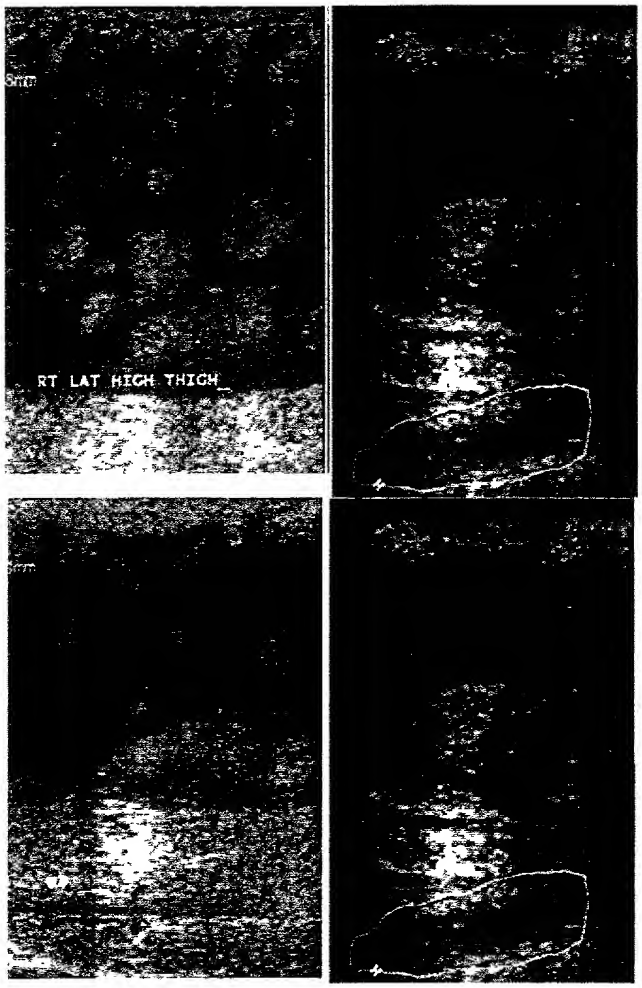


Figure 10

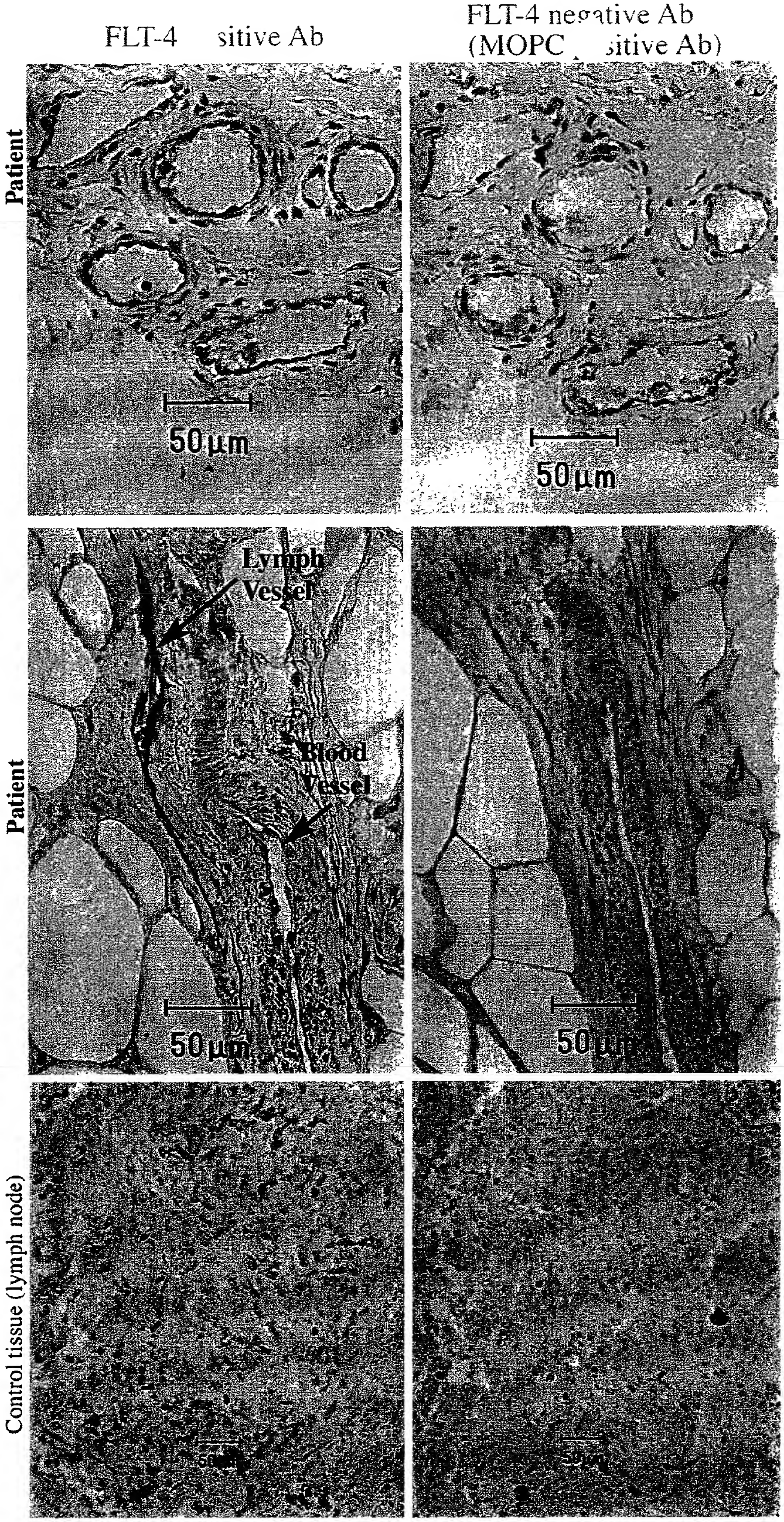

FLT-4 sitive Ab
FLT-4 negative Ab
(MOPC sitive Ab)
Patient
50 µm
50 µm
Patient
Lymph
Vessel
Blood
Vessel
50 µm
50 µm
Control tissue (lymph node)

Figure 11

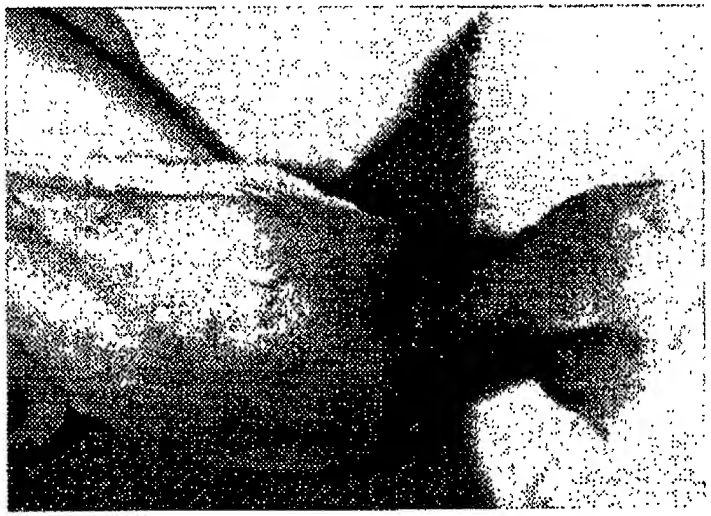


Fig. 12A

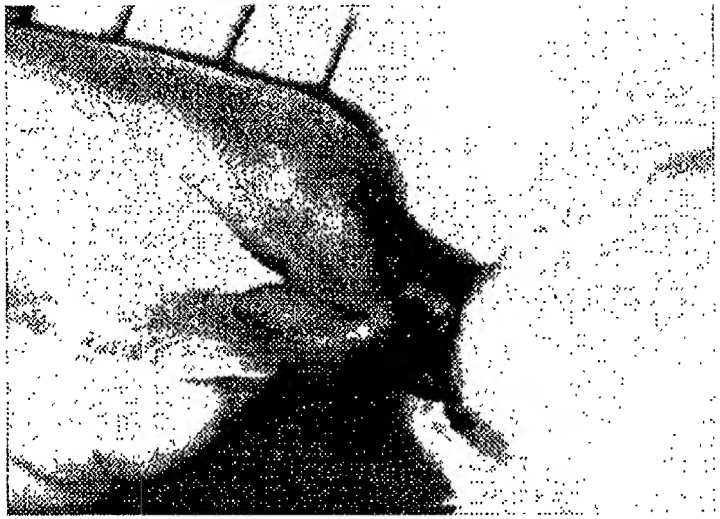


Fig 12B

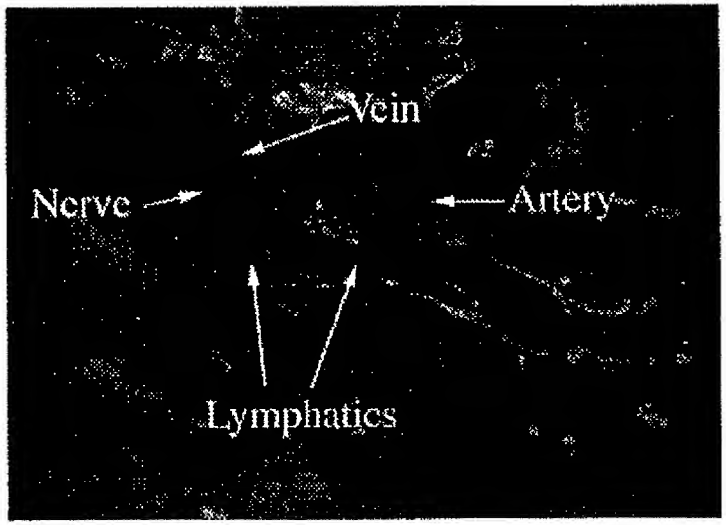
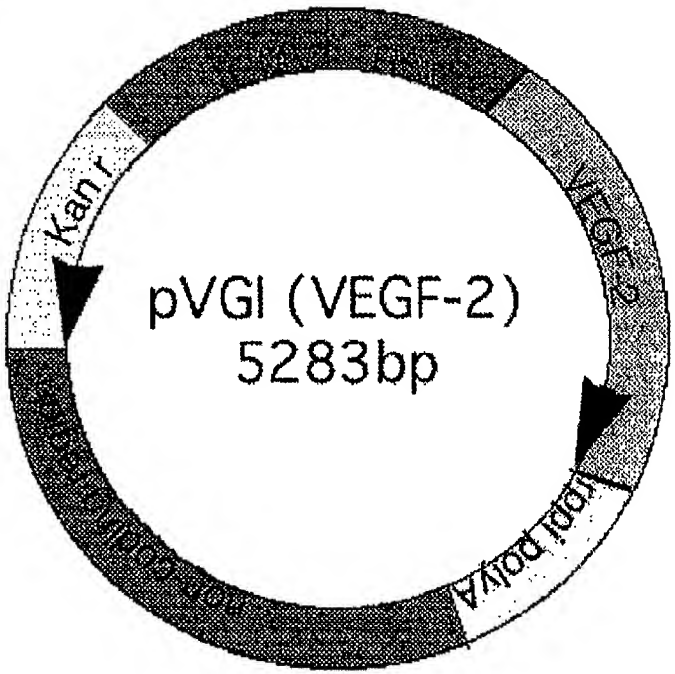


Fig. 12C

Fig. 13A



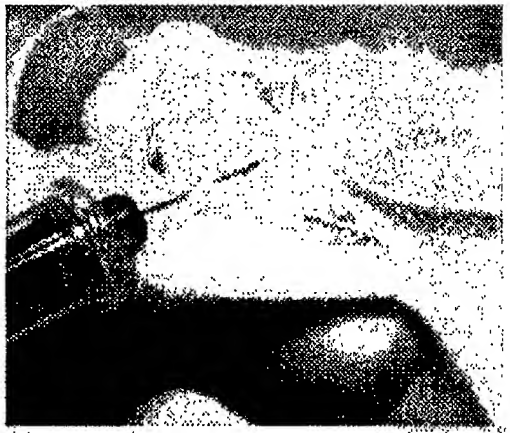
Intradermal and Subcutaneous

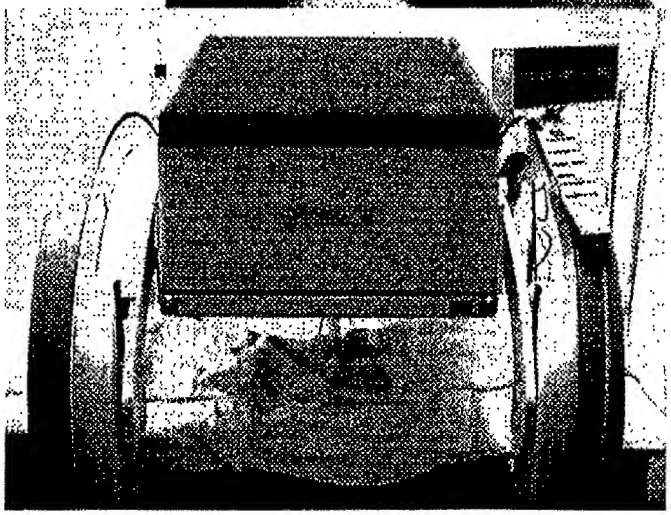
500ug

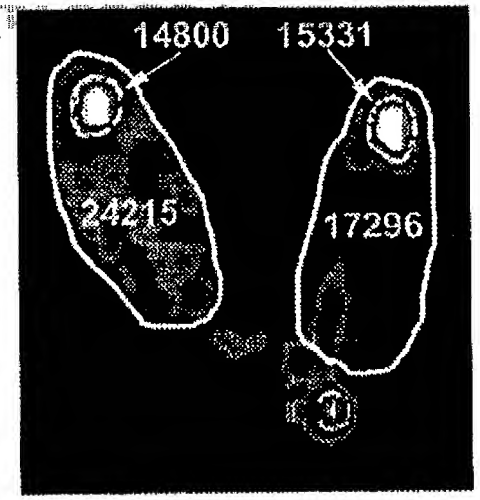
D1 D6 D11

Fig. 13B

Figs. 14 A-C

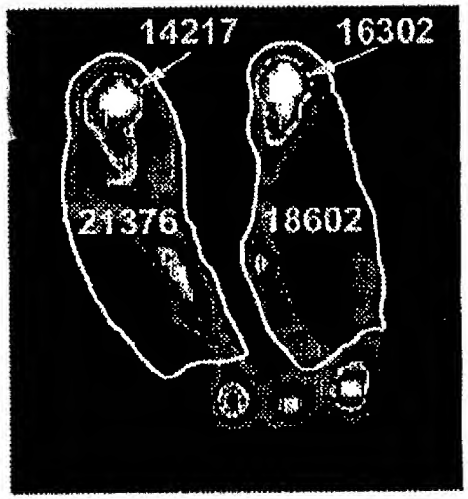






(24125-14800)/(17296-15331)
= 4.75

Fig. 15A



(21376-14217)/(18602-16302)
=3.11

Fig. 15B

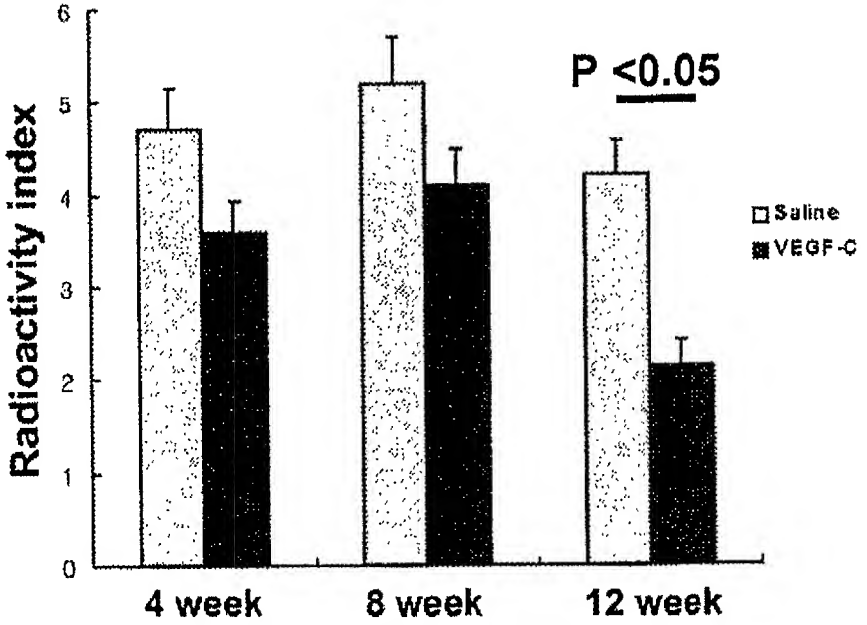


Fig. 15C

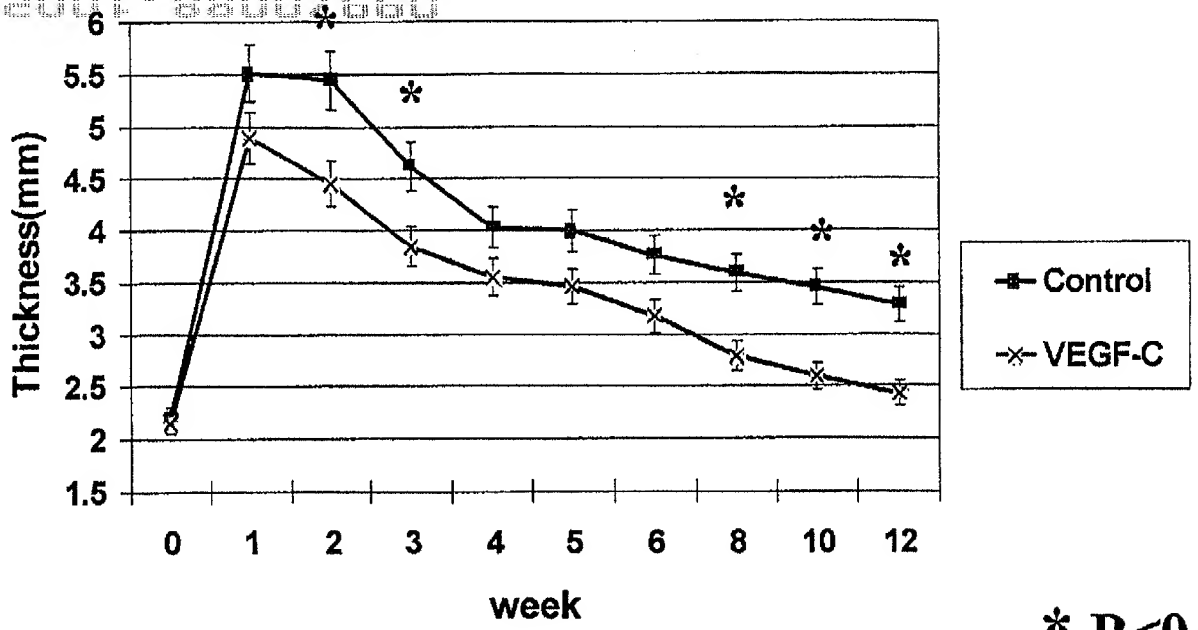


Fig. 16A

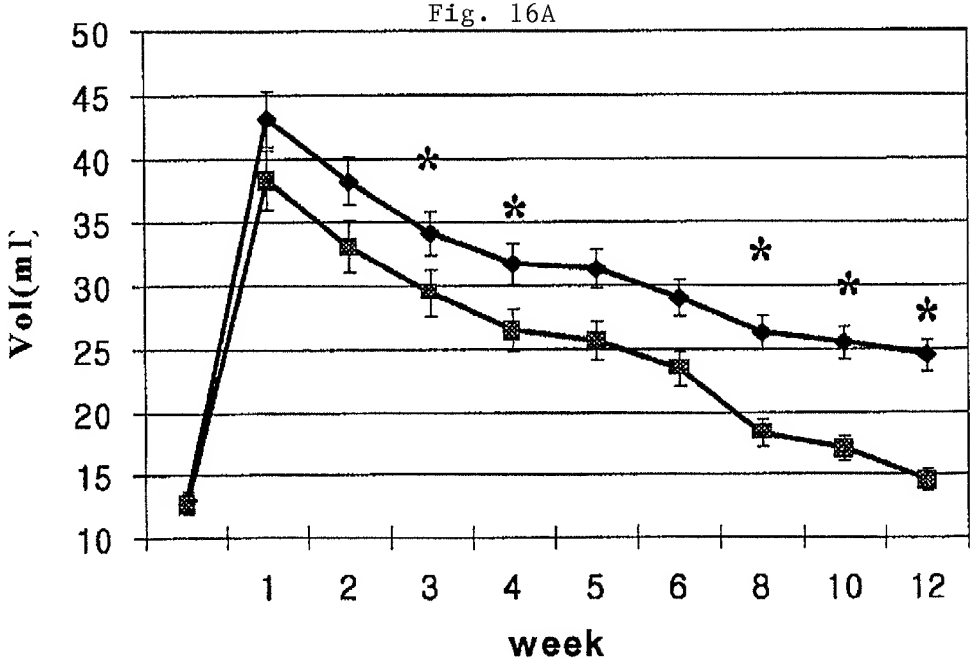


Fig. 16B

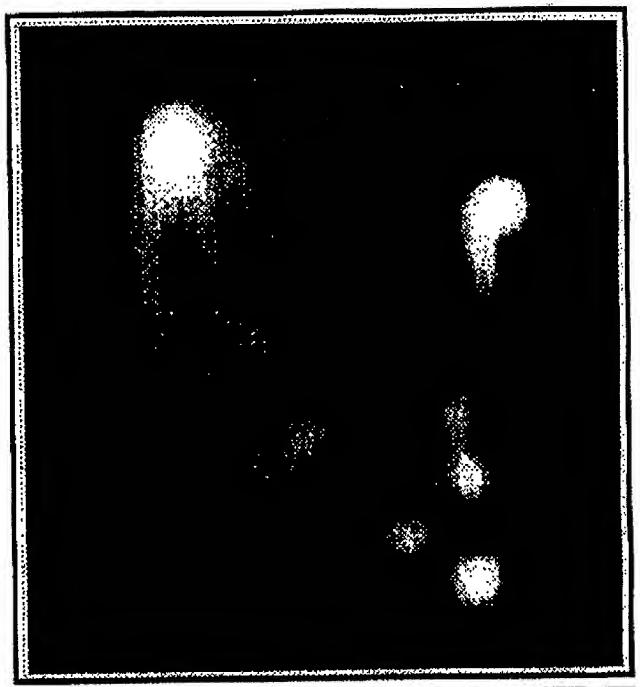
*** P<0.05**

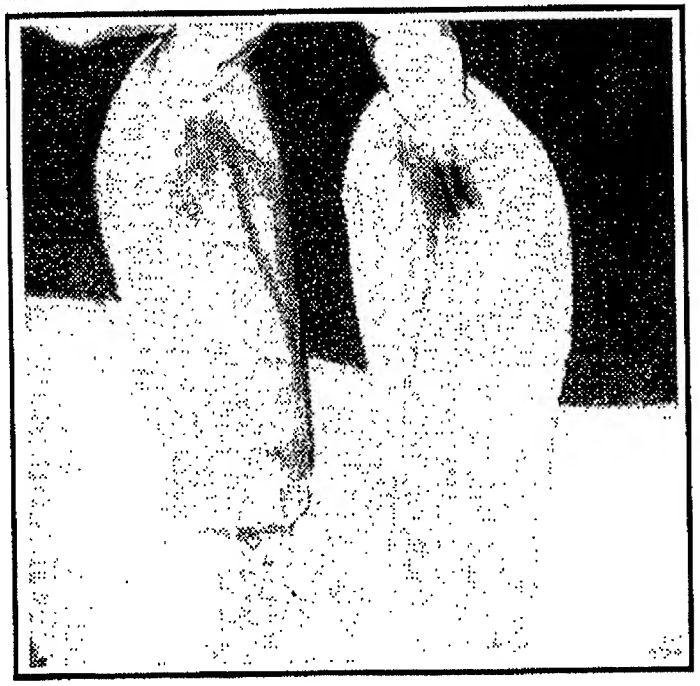
Figs. 17 A-B

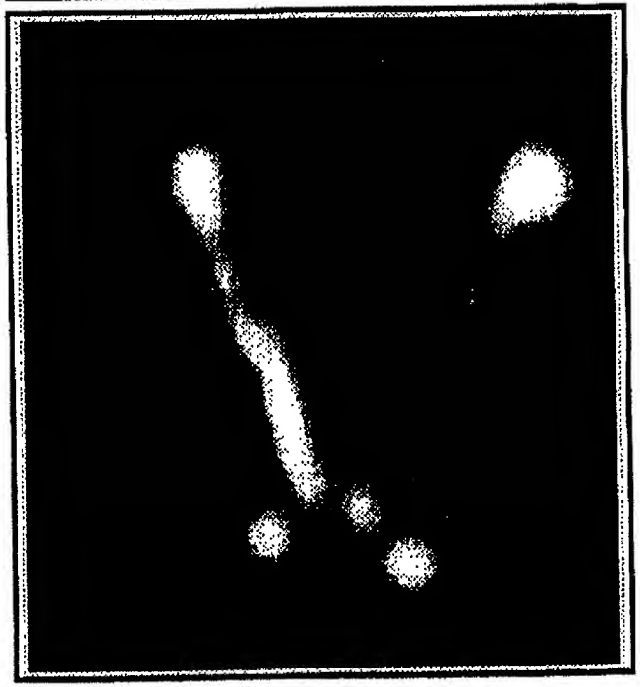
Figs. 17 C-D

Control

VEGF-C







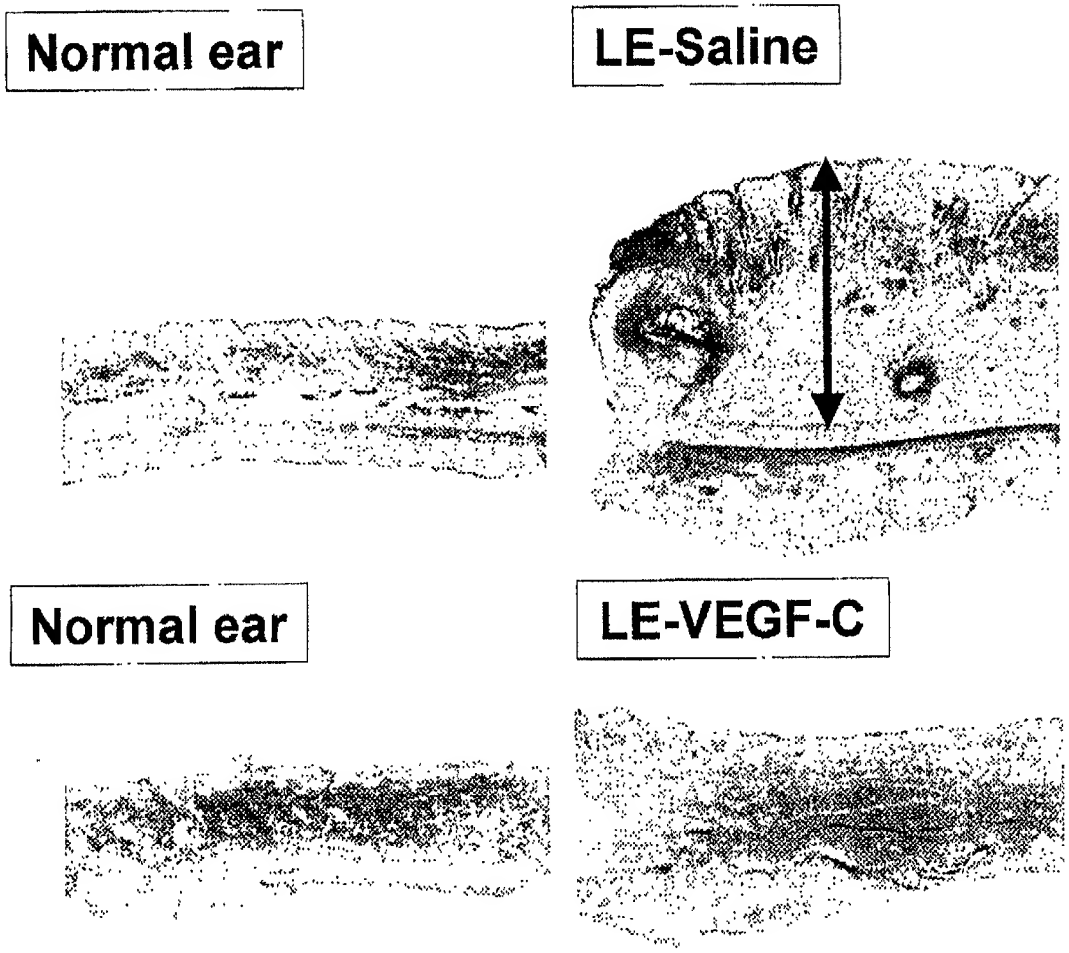


Fig. 18A

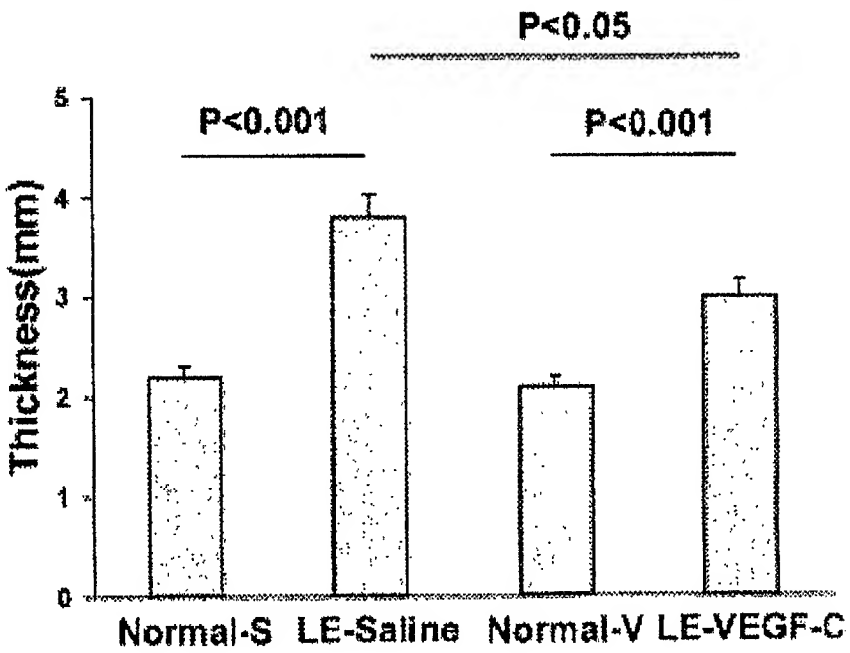
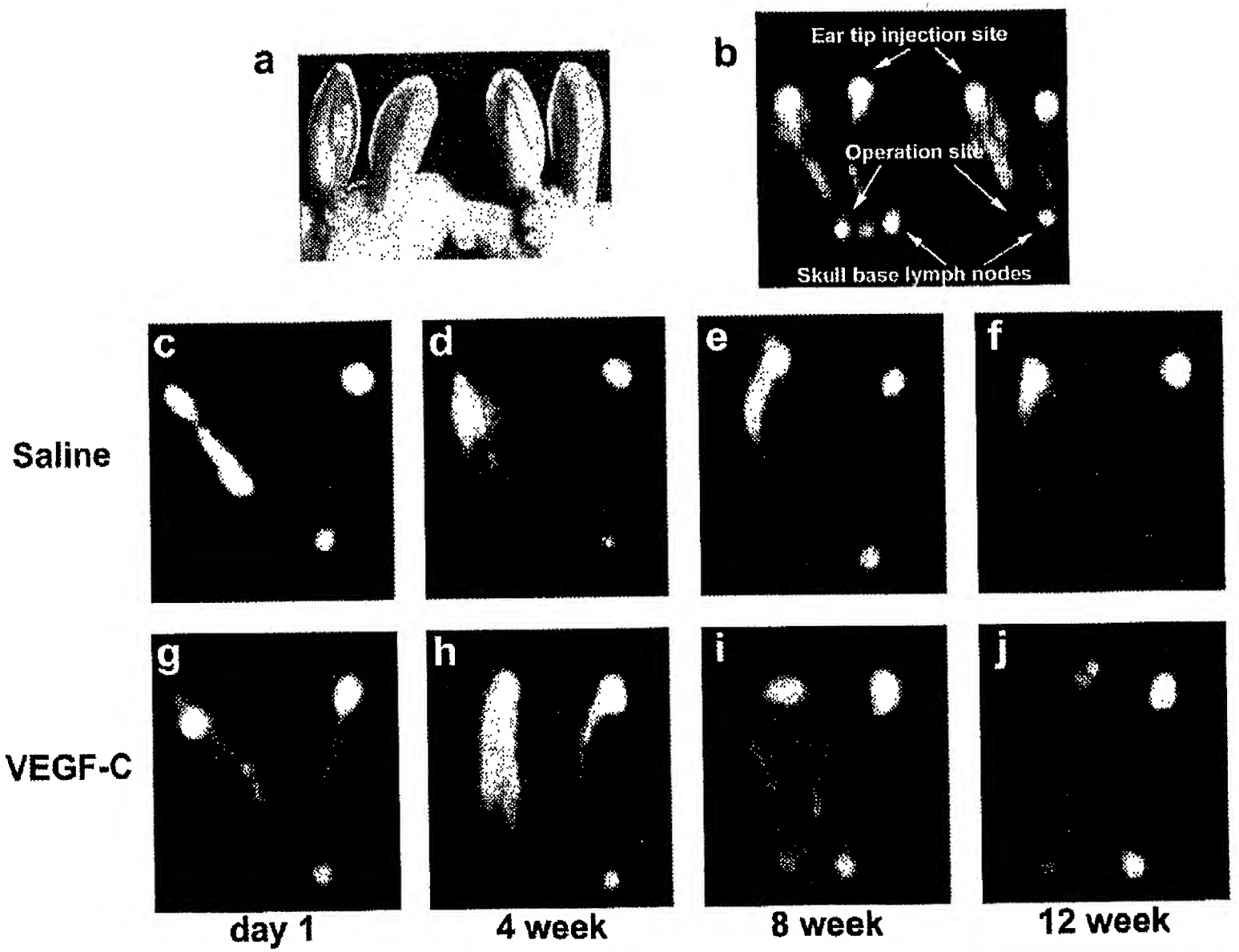


Fig. 18B



Figs. 19 A-J

Fig. 20A

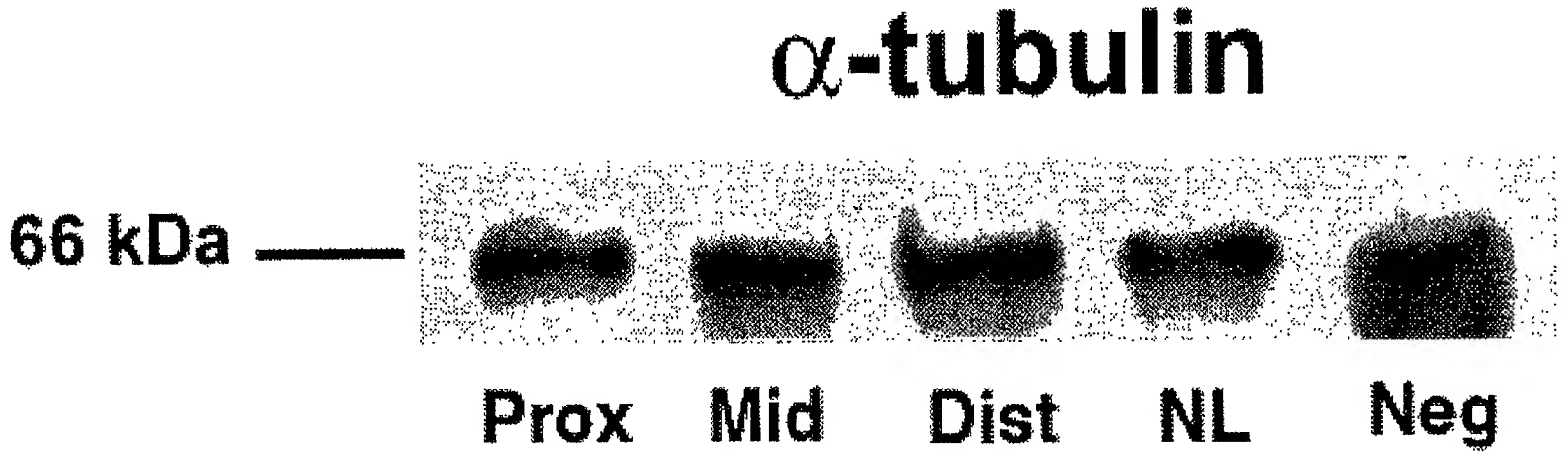
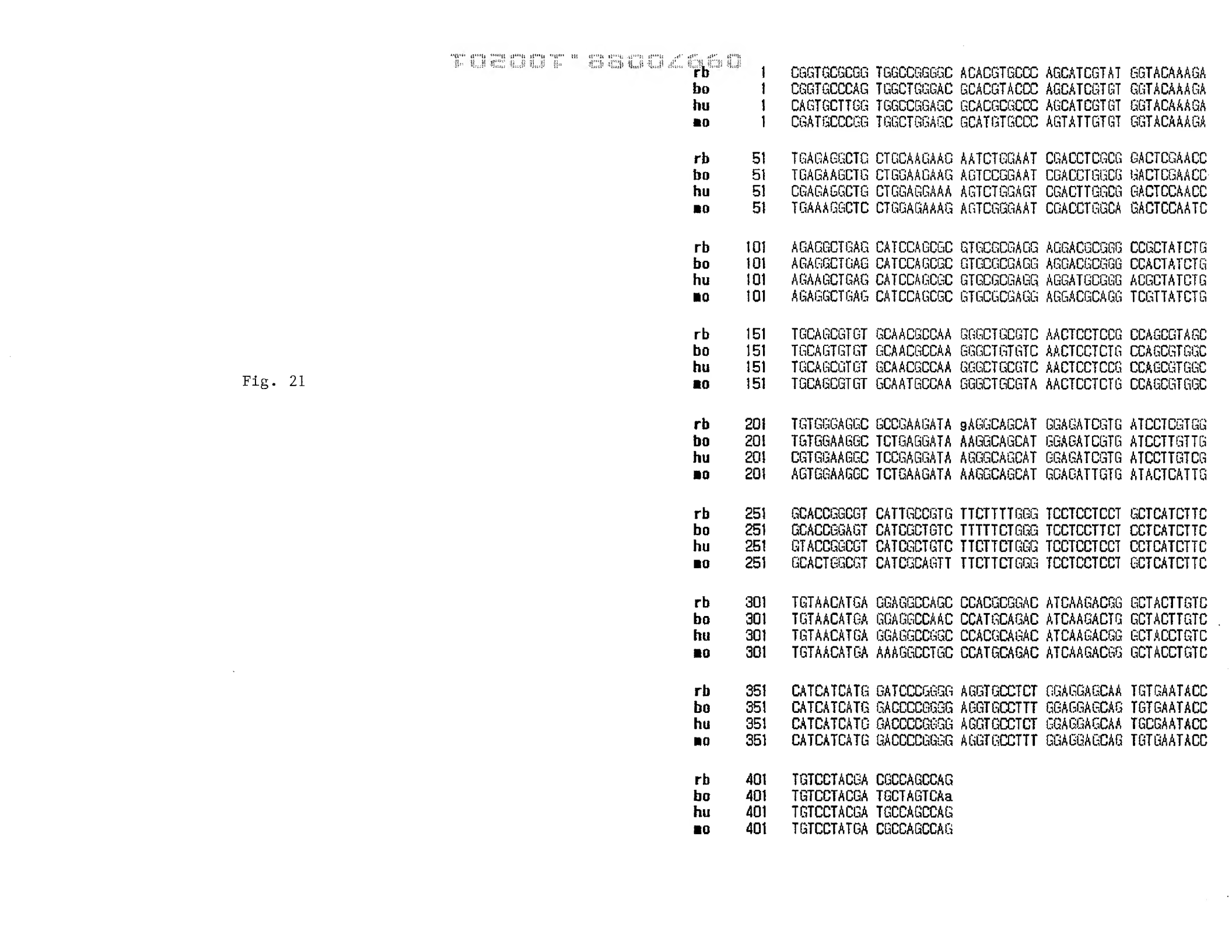


Fig. 20B



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bo    1   CGGTGCCCAG TGGCTGGGAC GCACGTACCC AGCATCGTGT GGTACAAAGA
hu    1   CAGTGCTTGG TGGCCGGAGC GCACGCGCCC AGCATCGTGT GGTACAAAGA
mo    1   CGATGCCCGG TGGCTGGAGC GCATGTGCCC AGTATTGTGT GGTACAAAGA

rb   51   TGAGAGGCTG CTGCAAGAAG AATCTGGAAT CGACCTCGCG GACTCGAACC
bo   51   TGAGAAGCTG CTGGAAGAAG AGTCCGGAAT CGACCTGGCG GACTCGAACC
hu   51   CGAGAGGCTG CTGGAGGAAA AGTCTGGAGT CGACTTGGCG GACTCCAACC
mo   51   TGAAAGGCTC CTGGAGAAAG AGTCGGGAAT CGACCTGGCA GACTCCAATC

rb  101   AGAGGCTGAG CATCCAGCGC GTGCGCGAGG AGGACGCGGG CCGCTATCTG
bo  101   AGAGGCTGAG CATCCAGCGC GTCGCCGAGG AGGACGCGGG CCACTATCTG
hu  101   AGAAGCTGAG CATCCAGCGC GTCGCCGAGG AGGATGCGGG ACGCTATCTG
mo  101   AGAGGCTGAG CATCCAGCGC GTGCGCGAGG AGGACGCAGG TCGTTATCTG

rb  151   TGCAGCGTGT GCAACGCCAA GGGCTGCGTC AACTCCTCCG CCAGCGTAGC
bo  151   TGCAGTGTGT GCAACGCCAA GGGCTGTGTC AACTCCTCTG CCAGCGTGGC
hu  151   TGCAGCGTGT GCAACGCCAA GGGCTGCGTC AACTCCTCCG CCAGCGTGGC
mo  151   TGCAGCGTGT GCAATGCCAA GGGCTGCGTA AACTCCTCTG CCAGCGTGGC

rb  201   TGTGGGAGGC GCCGAAGATA gAGGCAGCAT GGAGATCGTG ATCCTCGTGG
bo  201   TGTGGAAGGC TCTGAGGATA AAGGCAGCAT GGAGATCGTG ATCCTTGTTG
hu  201   CGTGGAAGGC TCCGAGGATA AGGGCAGCAT GGAGATCGTG ATCCTTGTCG
mo  201   AGTGGAAGGC TCTGAAGATA AAGGCAGCAT GCAGATTGTG ATACTCATTG

rb  251   GCACCGGCGT CATTGCCGTG TTCTTTTGGG TCCTCCTCCT GCTCATCTTC
bo  251   GCACCGGAGT CATCGCTGTC TTTTTCTGGG TCCTCCTTCT CCTCATCTTC
hu  251   GTACCGGCGT CATCGCTGTC TTCTTCTGGG TCCTCCTCCT CCTCATCTTC
mo  251   GCACTGGCGT CATCGCAGTT TTCTTCTGGG TCCTCCTCCT GCTCATCTTC

rb  301   TGTAACATGA GGAGGCCAGC CCACGCGGAC ATCAAGACGG GCTACTTGTC
bo  301   TGTAACATGA GGAGGCCAAC CCATGCAGAC ATCAAGACTG GCTACTTGTC
hu  301   TGTAACATGA GGAGGCCGGC CCACGCAGAC ATCAAGACGG GCTACCTGTC
mo  301   TGTAACATGA AAAGGCCTGC CCATGCAGAC ATCAAGACGG GCTACCTGTC

rb  351   CATCATCATG GATCCCGGGG AGGTGCCTCT GGAGGAGCAA TGTGAATACC
bo  351   CATCATCATG GACCCCGGGG AGGTGCCTTT GGAGGAGCAG TGTGAATACC
hu  351   CATCATCATG GACCCCGGGG AGGTGCCTCT GGAGGAGCAA TGCGAATACC
mo  351   CATCATCATG GACCCCGGGG AGGTGCCTTT GGAGGAGCAG TGTGAATACC

rb  401   TGTCCTACGA CGCCAGCCAG
bo  401   TGTCCTACGA TGCTAGTCAa
hu  401   TGTCCTACGA TGCCAGCCAG
mo  401   TGTCCTATGA CGCCAGCCAG
```

Fig. 21

```
rb   1   RCAVAGAHVP SIVWYKDERL LQEESGIDLA DSNQRLSIQR VREEDAGRYL
bo   1   RCPVAGTHVP SIVWYKDEKL LEEESGIDLA DSNQRLSIQR VREEDAGHYL
hu   1   QCLVAGAHAP SIVWYKDERL LEEKSGVDLA DSNQKLSIQR VREEDAGRYL
mo   1   RCPVAGAHVP SIVWYKDERL LEKESGIDLA DSNQRLSIQR VREEDAGRYL

rb   51  CSVCNAKGCV NSSASVAVgG AEDRGSMEIV ILVGTGVIAV FFWVLLLLIF
bo   51  CSVCNAKGCV NSSASVAVEG SEDKGSMEIV ILVGTGVIAV FFWVLLLLIF
hu   51  CSVCNAKGCV NSSASVAVEG SEDKGSMEIV ILVGTGVIAV FFWVLLLLIF
mo   51  CSVCNAKGCV NSSASVAVEG SEDKGSMEIV ILIGTGVIAV FFWVLLLLIF

rb   101 CNMRRPAHAD IKTGYLSIIM DPGEVPLEEQ CEYLSYDASQ
bo   101 CNMRRPtHAD IKTGYLSIIM DPGEVPLEEQ CEYLSYDASQ
hu   101 CNMRRPAHAD IKTGYLSIIM DPGEVPLEEQ CEYLSYDASQ
mo   101 CNMKRPAHAD IKTGYLSIIM DPGEVPLEEQ CEYLSYDASQ
```

Fig. 22A

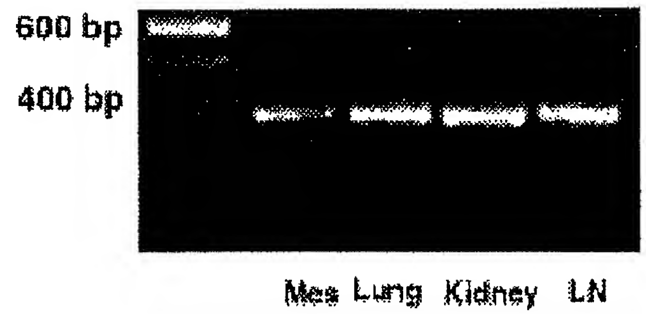


Fig. 22B

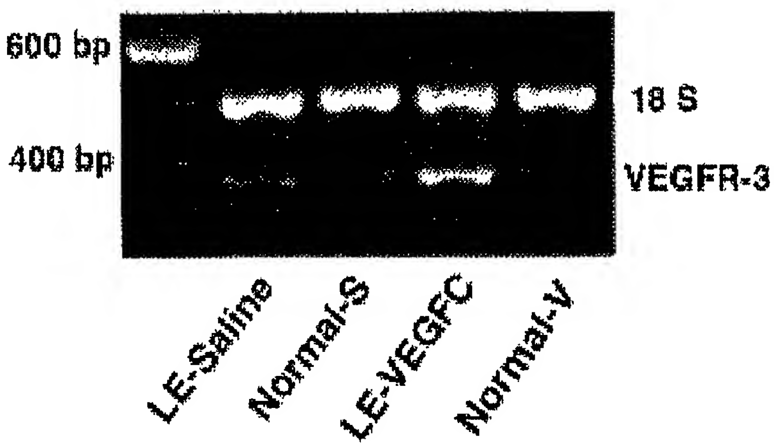


Fig. 22C

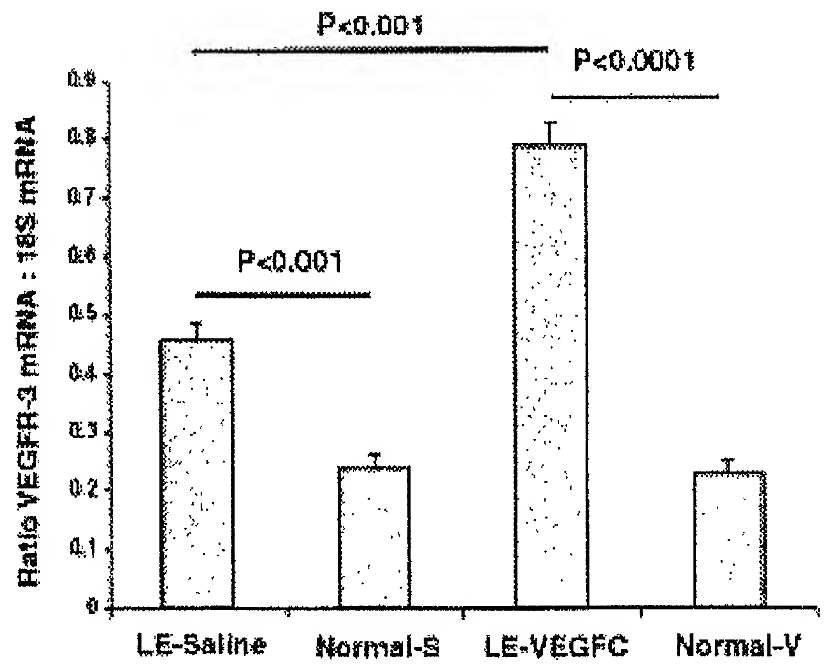


Fig. 22D

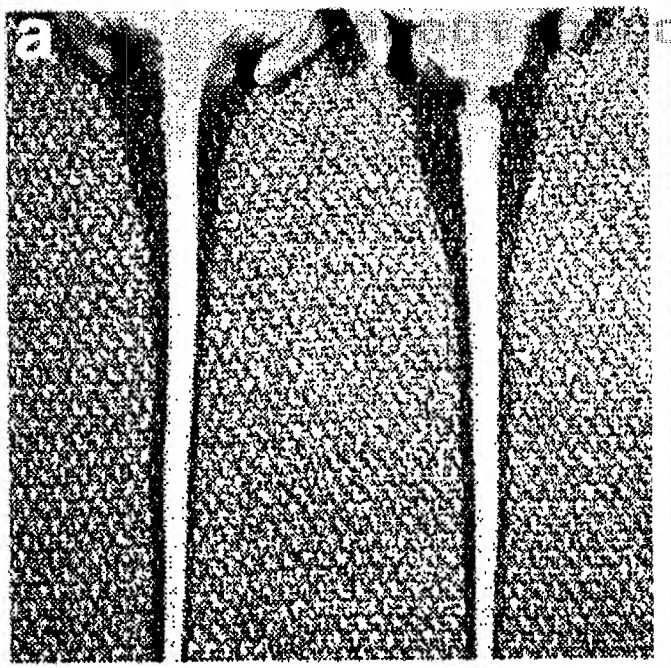


Fig. 23A

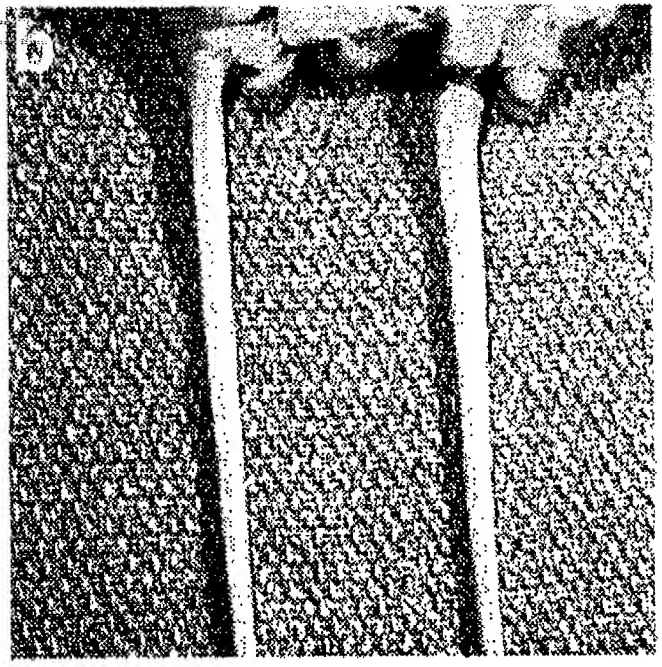


Fig. 23B

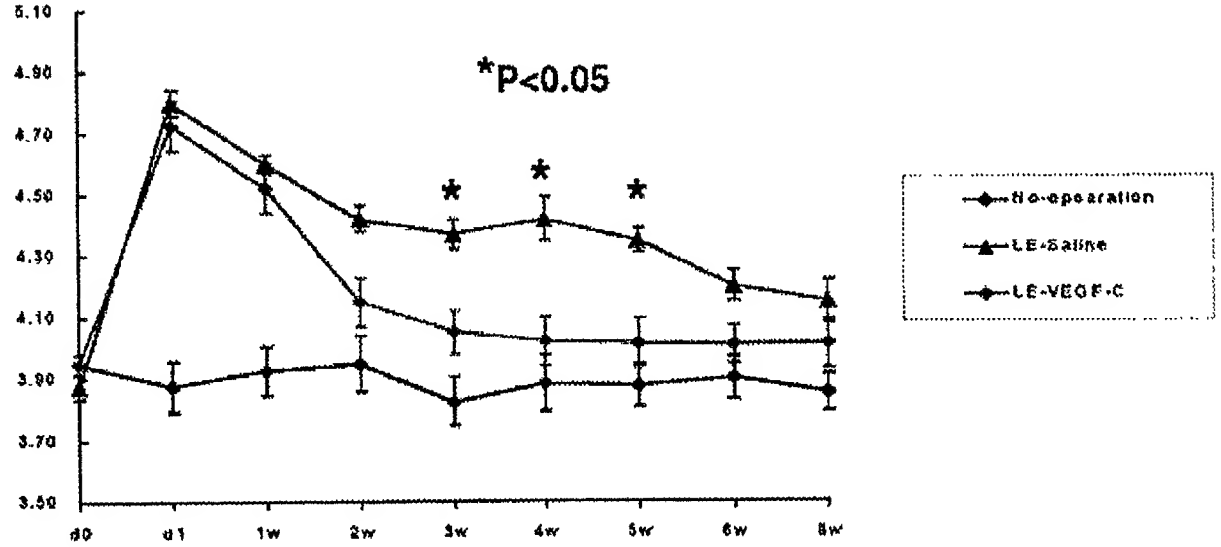
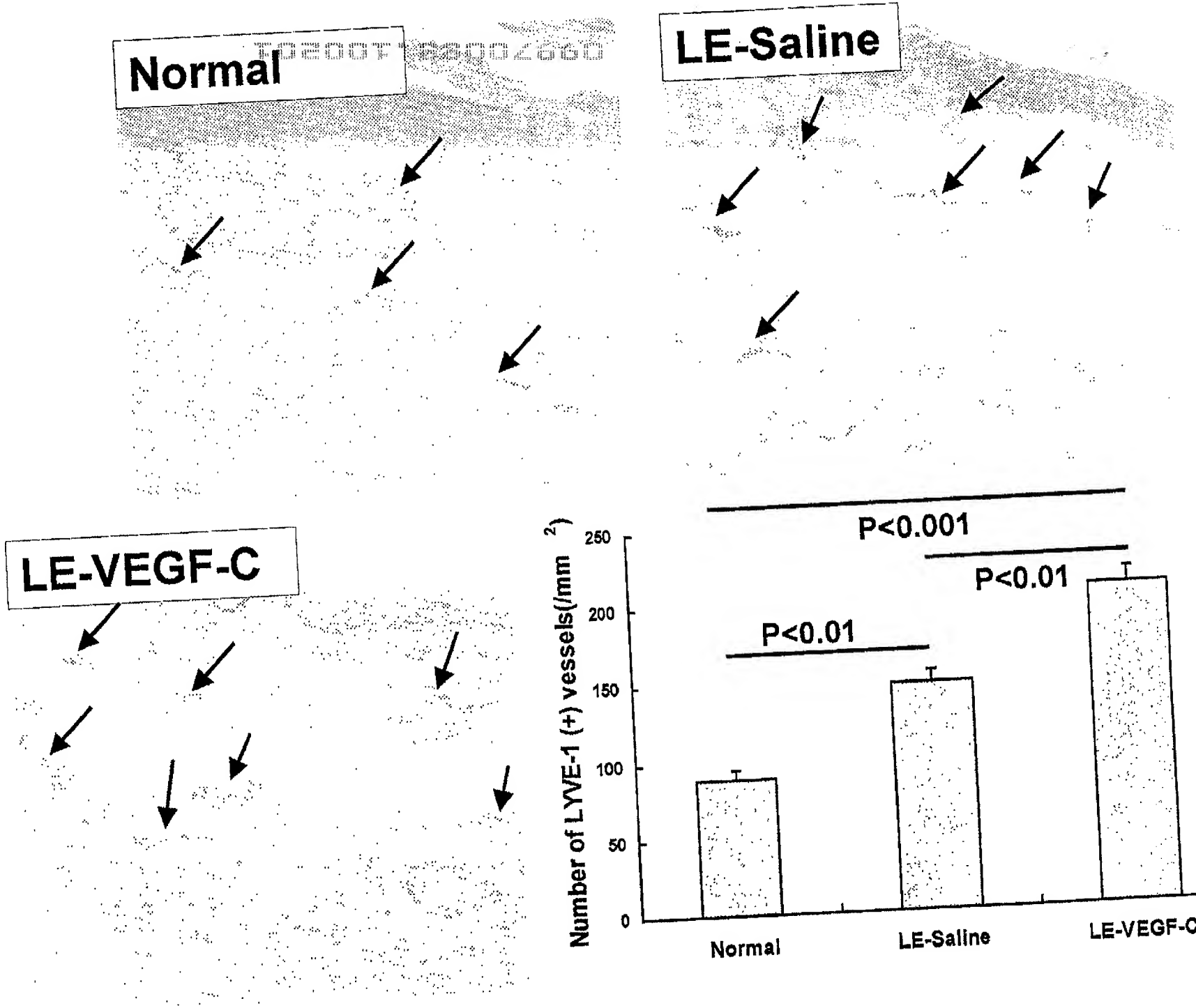


Fig. 23C

Fig. 24 A-D


Normal
LE-Saline
LE-VEGF-C
P<0.001
P<0.01
P<0.01
Number of LYVE-1 (+) vessels(/mm 2)
250
200
150
100
50
0
Normal
LE-Saline
LE-VEGF-C